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TOWNSEND and TOWNSEND and CREW LLP

By: Malinda Dogut

PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Sette *et al.*

Application No.: 08/452,843

Filed: May 30, 1995

For: HLA BINDING PEPTIDES AND THEIR USES

Examiner: Marianne DiBrino, Ph.D.

Art Unit: 1644

RESPONSE TO RESTRICTION REQUIREMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Communication mailed November 24, 1999, Applicants submit the Group election and election of species as detailed below with traverse. A petition to extend time for three months is enclosed.

Group Election

The Examiner has set forth two Groups defined as follows:

Group I, claims 67-75, 78-85, 89-116, 120-139, 142-154, and 157-165, drawn to a method for making a peptide wherein the preparing, providing or obtaining step comprises providing an amino acid sequence for the peptide.

Group II, claims 76-77, 86-88, 117-119, 140-141, and 155-156, drawn to methods for making a peptide using a nucleic acid that encodes the peptide.

The Requirement for an election of a Group is traversed. The two Groups set forth by the Examiner stem from a common concept and theory and are thus related. Accordingly, prosecution of all of the claims of Groups I and II together would not place a substantially greater burden on the Examiner.

Restriction of an application is discretionary, as a restriction requirement is made only to avoid placing an undue examination burden on the Examiner and the PTO. Where claims can be examined together without undue burden, the Examiner must examine the claims on the merits even though they are directed to independent and distinct inventions (MPEP § 803). In establishing that an "undue burden" would exist for co-examination of claims, the Examiner must show that examination of the claims would involve substantially different prior art searches, making the co-examination burdensome. Applicants submit that examination of the claims of Group I would not involve a substantially different prior art search than that required to examine all of the claims together. All of the claims relate to methods of making an immunogenic peptide comprising an epitope having a specified motif or residue pattern, which peptide induces a cytotoxic T cell response. Accordingly, a thorough search of the subject matter, *i.e.*, the motif-bearing immunogenic peptides, of Group I claims also overlaps with the subject matter of the Group II claims: the nucleic acids of Group II encode the immunogenic peptides of Group I. Thus, it would not impose an undue burden to search the subject matter of all of the claims together.

Based on these considerations, Applicants respectfully request that the Examiner withdraw the Restriction Requirement and consider the claims of Groups I and II together.

Formal election

As a formal matter, applicants elect Group I, 67-75, 78-85, 89-116, 120-139, 142-154, and 157-165, drawn to peptides. The election is traversed for the reasons set forth above.

Species Election

Overview

The pending claims are directed to methods of making immunogenic peptides. The Examiner has required election of a single species through multiple layers of specified characteristics. The myriad elections are traversed.

In order to facilitate an evaluation of the requirements set forth in Paper 24, a representative generic claim, for example claim 67, is presented below:

> 67. A method for making an immunogenic peptide comprising an epitope consisting of about 8-11 amino acid residues that comprises an HLA B7 supermotif, and that binds to an HLA molecule and induces a cytotoxic T cell response, said method comprising steps of:
>
> (a) providing an amino acid sequence of an antigen of interest;
>
> (b) identifying within said sequence a putative T cell epitope, wherein said putative epitope consists of about 8-11 amino acid residues and is identified by the presence of an HLA-B7 structural supermotif associated with peptide binding to multiple HLA molecules, said structural supermotif comprising a first amino acid anchor residue at position two from the epitope's N-terminal residue, said first anchor residue selected from the group consisting of P, and a second anchor residue selected from the group consisting of V, I, L, F, M, W, Y, and A as the epitope's carboxyl-terminal amino acid residue;
>
> (c) preparing one or more peptide fragments of said antigen of interest that comprise the HLA B7 structural supermotif;
>
> (d) testing a first complex of said one or more motif-bearing peptide fragments and a first HLA molecule for an ability to be recognized by HLA-restricted cytotoxic T cells, and to thereby induce a cytotoxic T cell response to the epitope;
>
> (e) testing at least a second complex of said one or more motif-bearing peptide fragments and at least a second HLA molecule for an ability to be recognized by HLA-restricted cytotoxic T cells, and to thereby induce a cytotoxic T cell response to the epitope; and
>
> (f) selecting said one or more peptide fragments comprising the HLA-B7 structural supermotif that induce a cytotoxic T cell response to the epitope, when the epitope is in the first complex and when the epitope is in the at least a second complex.

As discussed in more detail below, Applicants submit that the multi-layered species election set forth in Paper 24 disregards key aspects of the invention and does not provide for examination of the invention as disclosed and claimed by the Applicants. Although some type of species election may be reasonable under the circumstances, the election requirements of Paper 24 are not. A reasonable species election should be based on the invention as disclosed and as claimed by the Applicants in the generic claims. Accordingly, any species election should focus on the elements provided in those claims, which relate to an HLA class I supermotif pattern of amino acid residues that is associated with binding multiple specified HLA molecules. Any appropriate species are delineated by one or more patterns defined by the claimed supermotif. Accordingly, Applicants propose that an appropriate species election should be directed to species encompassed by a defined amino acid of P at a position two of an epitope together with the collective examination of the amino acid residues that have been defined for the supermotif at the C-terminus of an epitope. Moreover, the proposed election does not present an undue burden for the Examiner.

The species election requirement as set forth is also extremely confusing. It does not apprise the Applicants how examination of the claims will proceed once an initial species is selected and is determined to be free of the prior art, nor does it enlighten the Applicants as to the strategies that might be employed to make elections. The Applicants thus have no assurance that the invention as they have disclosed and claimed it will be examined. Additionally, the use of "where applicable" is not clear.

Discussion

The election of species detailed in Paper 24 requires the Applicants to elect a representative from the extensive list of the following criteria:

a.) a peptide disclosed in the specification ; and

b.) a peptide that is encompassed by a particular motif; and

c.) a peptide of a specific length, *i.e.*, 8, 9, 10, 11 or greater than 11 residues; and

e.) a cancer-associated antigen or a pathogen-derived peptide; and

f.) if a cancer-associated antigen is selected, one patentably distinct species of antigen; or if a pathogen-derived peptide is selected, one patentably distinct species of antigen; and

g.) a method where the testing step occurs *in vivo* or *in vitro*, and where the determining whether the peptide is immunogenic step occurs *in vivo* or *in vitro*, and the contacting step occurs *in vivo* or *in vitro*; and

h.) a method wherein the identifying a peptide that has an IC_{50} of a specified value step or the determining binding affinity step involves one of the HLA molecules recited in claims 70 and 71; and

i.) a method wherein the contacting step or the testing step comprises contacting a CTL-restricted to one of the allele-specific HLA molecules listed in section 11 of Paper 24.

Applicants respectfully submit that the incredibly detailed dissection of the claimed subject matter is not justified. The species election requires that Applicants make choices that are directed to mere characteristics of embodiments and detract from the actual invention, *i.e.*, methods of making an immunogenic peptide comprising an epitope defined by a supermotif associated with binding to multiple HLA molecules, intended by Applicants to be the focus of their application as properly claimed by the Applicants in their independent claims. A less onerous species election could have been required, and no unduly extensive and burdensome search would be necessary (MPEP § 808.01(a)). Accordingly, as will be explained, the claims should be examined as a whole or in a far less dissected manner.

A. The multi-layered election of species is confusing.

Applicants find the species election extremely confusing. The use of the term "where applicable" is not clear. Are the Applicants to decide whether or not the particular requirement should apply? Moreover, Applicants have not been able to ascertain how the Examiner will proceed with the examination of the application upon a determination that an initially elected "species" that conforms to all of the election requirements is free of the prior art. Will the determination of the next species to be examined be made based on the sequence of the peptide, the length of the peptide, the antigen from which the peptide is derived, the HLA molecule(s) to which the peptide binds, whether the various steps, "if applicable", occur

in vitro or *in vivo*, *etc.*? This presents a major concern to the Applicants because they are not able to ascertain basic parameters of the examination and thus determine a suitable prosecution strategy. Furthermore, each time a new species is selected, various aspects of the invention are omitted at what seems to be an arbitrary choice of the Examiner (discussed in Section B., below). Under the traversed requirement of Paper 24, the ultimate nature of the invention thus appears to be defined not by the Applicants, but by the Examiner. Hence, it is evident that implementation of the species election requirements imposed by the Examiner would cause the loss of Applicants' right to pursue their invention as claimed and, thus, should be withdrawn.

B. Examination of a single species with multiple levels of characteristics conforming to the election requirements disregards important aspects of the invention as claimed.

It is improper for the Office to refuse to examine that which applicants regard as their invention (MPEP § 803.02, relating to Markush claims). Though the subject restriction requirement is for a species election which does not *per se* preclude examination of the scope of the generic claims in this application, the multi-layered species election could have undue and harsh consequences. The dissection of the claims in the manner of the Office Action could potentially prolong prosecution by directing focus to less critical characteristics that may not even be significant elements of the actual invention. For example, where a single peptide is examined, the "supermotif" aspect of the invention is not being examined. The supermotif is a key aspect of Applicants' invention as reflected by the generic independent claims. "[T]he scope of subject matter of an invention is governed not by the examiner's conception of the invention, but by that which the applicant regards as his invention" *In re Wolfrum* 179 USPQ 620 (C.C.P.A. 1973) (addressing a 35 U.S.C. § 112 rejection).

Thus, Applicants maintain that requiring election among numerous characteristics set forth in Paper 24 ignores critical aspects of the invention as disclosed and claimed in the generic claims, such as claim 67 provided above. The generic claims relate to methods of making immunogenic peptides that are conceptually bound together by a commonality of function, operation and effect. The claimed methods are directed to an immunogenic peptide comprising an epitope *having a specified supermotif or residue pattern associated with binding to multiple HLA molecules, wherein the peptide is immunogenic and*

induces a cytotoxic T cell response in the context of the multiple HLA molecules to which the peptide binds. Thus, Applicants' invention is truly generic in that it covers supermotif patterns present in any peptide sequence that can be bound by multiple HLA molecules and thereafter induce CTL responses, and is appropriately examined on a generic level. The claimed invention is not simply a list of methods of making immunogenic peptides of unrelated sequences and is not in any way constrained by parameters such as antigenic source or length of an HLA Class I epitope (as discussed in detail at a recent Examiner interview with Examiners Schwartz, Chan, Schwadron and former Examiner Cunningham). Consequently, the dissection of the invention by the multi-layered election requirement loses sight of the actual invention and is tantamount to a recharacterization of the invention.

Applicants also respectfully point out that the examination of claims in the pending application based on the species election set forth in Paper 24 can yield results that are incongruous with the policy set forth in the MPEP at § 803.04. Although MPEP § 803.04 is directed to nucleic acids and the claims of the present application are directed to peptides, the same principles are at issue: the species election requirement could result in the examination of a fewer number of actually related sequences than if the claims were such that they fell within the policies of MPEP § 803.04 and were sequences that were completely unrelated.

The generic claims in this case focus on amino acid supermotif patterns present in immunogenic peptide epitopes. Accordingly, Applicants propose that it would be appropriate to make a species election requirement based on the elements provided in the generic claim, namely of species defined by one or more supermotif patterns, in accordance with MPEP § 803.02. A species election consonant with MPEP policies would involve election of individual species as follows: a species encompassed by the specific amino acid P at residue two of an epitope together with the amino acid residues that have been defined for the supermotif at a C-terminus of an epitope (V, I, L, F, M, W, Y, or A, at one of positions 8, 9, 10, or 11). Examination of the supermotif in this manner provides for not more than 32 species. Thus, this proposed species election requirement is properly directed to the motif aspect of the invention set forth by the generic claims and focuses on the invention as a whole.

C. No undue examination burden is imposed by examining all C-terminal positions together.

Furthermore, for a given supermotif, no undue examination burden is imposed by examining P at position two and V, I, L, F, M, W, Y, or A residue at each of positions 8, 9, 10, and 11, *i.e.*, the C- terminus of HLA class I epitopes. Computer searching techniques readily permit the searching of amino acid sequences with designated amino acids at positions of choice. Such a search is not unduly extensive, but is thorough and properly includes the relevant supermotif species of a P residue at a position two and any of V, I, L, F, M, W, Y, or A at the C terminal position of an epitope. The species defined in this manner number no more than 8. Moreover, for teachings related to peptides that bind to HLA class I molecules, it is prudent to consider C-terminal positions of epitopes which are 8, 9, 10, or 11 residues long, to get a truly comprehensive view of this art. Logic dictates that a typical computer search of the claimed supermotif would necessarily reveal any art related to methods of making immunogenic peptides of different lengths. The search would also reveal that HLA class I supermotif technology is not tied to any particular antigen, whether a cancer-associated antigen or a pathogenic agent and furthermore, certainly would not be restricted by the other multitudinous characteristics set forth in Paper 24.

The species election detailed in the Paper 24 results in a division of Applicants' actual invention into an artificially voluminous and unreasonable number of "species" or more accurately, characteristics. An election requirement that defines a species as a method of making an immune peptide comprising an epitope characterized by a supermotif pattern associated with binding to multiple HLA molecules constitutes a "reasonable number" of species for examination, and thereby balances the rights of the inventor and the administrative concerns of the Patent Office. An appropriate number of species, as discussed above, is: (i) 32, *i.e.*, P at position two of an epitope in combination with each residue (V, I, L, F, M, W, Y, or A) at a C-terminal position of an epitope of 8, 9, 10, or 11 in length; or (ii) more appropriately 8, *i.e.*, P at position two and each residue defined for the C-terminal position of an epitope.

D. Election

As a formal matter, Applicants elect the following species with the understanding that upon the determination that the elected species is free of the prior art,

additional species will be examined in accordance with MPEP § 803.02, which states that "should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended." and that "The prior art search will be extended to the extent necessary to determine the patentability of the Markush-type claim."

Accordingly, as a formal matter, Applicants elect:

the peptide APAPAPSWPL (*see, e.g.*, page 26, Table 5) and the motif P at position 2 and L at the carboxy terminal position; and a peptide of 10 residues in length; and an antigen of interest that a cancer-associated antigen, and an antigen that is p53; and the following regarding the requirements of section 9 of Paper 24:

claim 67, *in vitro* testing,

claim 80, *in vitro* contacting,

claim 84, *in vivo* testing,

claim 115, *in vitro* determining,

claim 116, *in vivo* contacting,

claim 137, *in vivo* complexing and *in vivo* contacting,

claim 139, *in vivo* determining,

claim 150 *in vivo* complexing, *in vivo* contacting,

claim 152, *in vitro* determining,

claim 159, *in vivo* complexing, *in vivo* contacting; and

an IC_{50} of "a specified value" for an HLA-B0701 molecule; and

a method wherein the contacting step or the testing step comprises contacting a CTL restricted to HLA-B0701 with a complex of a peptide and one of HLA-B0701.

All of the species elections are made with traverse for the reasons set forth herein. The pending claims that read on the elected species are 67-75, 78, 80-82, 84, 85, 89, 90, 92, 101, 103, 104-110, 112-116, 120, 121, 123, 132, 134-139, 142-146, 148-154, and 157-164.

CONCLUSION

If the Examiner has any questions regarding this communication, or if the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200 or the in-house Attorney for Applicants Timothy J. Lithgow at 858-860-2514.

Respectfully submitted,

Jean M. Lockyer
Reg. No. 44,879

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (415) 576-0200
Fax: (415) 576-0300
JML
SF 1079799 v1